

U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE FORM PTO-1390 (Modified) (REV 11-2000)		ATTORNEY'S DOCKET NUMBER 112843-044
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U S APPLICATION NO. (IF KNOWN, SEE 37 CFR 10/089658
INTERNATIONAL APPLICATION NO PCT/EP00/08995	INTERNATIONAL FILING DATE 14 September 2000	PRIORITY DATE CLAIMED 7 October 1999
TITLE OF INVENTION NUTRITIONAL COMPOSITION		
APPLICANT(S) FOR DO/EO/US Berger et al.		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
<ol style="list-style-type: none"> 1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)) The submission must include items (5), (6), (9) and (24) indicated below. 4. <input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371 (c) (2)) <ol style="list-style-type: none"> a. <input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> has been communicated by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US) 6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). <ol style="list-style-type: none"> a. <input type="checkbox"/> is attached hereto. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4). 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3)) <ol style="list-style-type: none"> a. <input checked="" type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)). 10. <input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)). 11. <input checked="" type="checkbox"/> A copy of the International Preliminary Examination Report (PCT/IPEA/409). 12. <input checked="" type="checkbox"/> A copy of the International Search Report (PCT/ISA/210). 		
Items 13 to 20 below concern document(s) or information included: <ol style="list-style-type: none"> 13. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 14. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 15. <input checked="" type="checkbox"/> A FIRST preliminary amendment 16. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 17. <input type="checkbox"/> A substitute specification. 18. <input type="checkbox"/> A change of power of attorney and/or address letter. 19. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825. 20. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4). 21. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4). 22. <input checked="" type="checkbox"/> Certificate of Mailing by Express Mail 23. <input checked="" type="checkbox"/> Other items or information 		
Return Receipt Postcard Express Mail Label No.: EL 727 382 421 US		

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 10/089658	INTERNATIONAL APPLICATION NO PCT/EP00/08995	ATTORNEY'S DOCKET NUMBER 112843-044																
24. The following fees are submitted:		CALCULATIONS PTO USE ONLY																
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) : <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%; padding: 2px;"><input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO</td> <td style="width: 20%; text-align: right; padding: 2px;">\$1040.00</td> </tr> <tr> <td><input checked="" type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO</td> <td style="text-align: right; padding: 2px;">\$890.00</td> </tr> <tr> <td><input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO</td> <td style="text-align: right; padding: 2px;">\$740.00</td> </tr> <tr> <td><input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)</td> <td style="text-align: right; padding: 2px;">\$710.00</td> </tr> <tr> <td><input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)</td> <td style="text-align: right; padding: 2px;">\$100.00</td> </tr> </table>		<input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	\$1040.00	<input checked="" type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	\$890.00	<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	\$740.00	<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	\$710.00	<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	\$100.00	ENTER APPROPRIATE BASIC FEE AMOUNT = \$890.00						
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Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)).		<input type="checkbox"/> 20 <input type="checkbox"/> 30 \$0.00																
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 25%;">CLAIMS</th> <th style="width: 25%;">NUMBER FILED</th> <th style="width: 25%;">NUMBER EXTRA</th> <th style="width: 25%;">RATE</th> </tr> </thead> <tbody> <tr> <td>Total claims</td> <td>25 - 20 =</td> <td>5</td> <td>x \$18.00</td> </tr> <tr> <td>Independent claims</td> <td>5 - 3 =</td> <td>2</td> <td>x \$84.00</td> </tr> <tr> <td colspan="3">Multiple Dependent Claims (check if applicable).</td> <td style="text-align: right;"><input type="checkbox"/> \$0.00</td> </tr> </tbody> </table>		CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	Total claims	25 - 20 =	5	x \$18.00	Independent claims	5 - 3 =	2	x \$84.00	Multiple Dependent Claims (check if applicable).			<input type="checkbox"/> \$0.00	TOTAL OF ABOVE CALCULATIONS = \$1,148.00
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE															
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Multiple Dependent Claims (check if applicable).			<input type="checkbox"/> \$0.00															
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27) The fees indicated above are reduced by 1/2		\$0.00																
		SUBTOTAL = \$1,148.00																
Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492 (f))		<input type="checkbox"/> 20 <input type="checkbox"/> 30 + \$0.00																
		TOTAL NATIONAL FEE = \$1,148.00																
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).		<input type="checkbox"/> \$0.00																
		TOTAL FEES ENCLOSED = \$1,148.00																
		<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 2px;">Amount to be: refunded</td> <td style="width: 50%; padding: 2px;">\$</td> </tr> <tr> <td colspan="2" style="padding: 2px;">charged</td> <td style="padding: 2px;">\$</td> </tr> </table>	Amount to be: refunded	\$	charged		\$											
Amount to be: refunded	\$																	
charged		\$																
<p>a. <input checked="" type="checkbox"/> A check in the amount of \$1,148.00 to cover the above fees is enclosed.</p> <p>b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No 02-1818 A duplicate copy of this sheet is enclosed.</p> <p>d. <input type="checkbox"/> Fees are to be charged to a credit card WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.</p>																		
<p>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</p> <p>SEND ALL CORRESPONDENCE TO:</p> <div style="border: 1px solid black; padding: 5px; margin-left: 10px;"> Robert M. Barrett, Esq. ATTORNEYS FOR APPLICANTS Bell, Boyd & Lloyd LLC P.O. Box 1135 Chicago, Illinois 60690-1135 </div>																		
 SIGNATURE																		
Robert M. Barrett <hr/> NAME <hr/> 30,142 <hr/> REGISTRATION NUMBER <hr/> March 28, 2002 <hr/> DATE																		

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Berger et al.
Appl. No.: PCT/EP00/08995
Filed: Filed Herewith
Title: NUTRITIONAL COMPOSITION
Art Unit: Unknown
Examiner: Unknown
Docket No.: 112843-044

Commissioner for Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

Sir:

Please amend the above-identified patent application as follows:

In the Specification:

Please delete lines 1-3 and substitute therefor:

--SPECIFICATION

TITLE OF THE INVENTION

“NUTRITIONAL COMPOSITION”--

On page 5, line 23, please add the following:

--SUMMARY OF THE INVENTION

The present invention provides improved nutritional and therapeutic compositions.--

On page 9, please delete lines 18-19 and substitute therefor:

--Additional features and advantages of the present invention will be described in and apparent from the detailed description of the presently preferred embodiments and the figures.

BRIEF DESCRIPTION OF THE DRAWINGS--

On page 10, line 19, please insert the following:

--DETAILED DESCRIPTION OF THE INVENTION

The present invention provides improved nutritional compositions. These compositions provide therapeutic benefits. The compositions include a naturally occurring precursor that is metabolized to a compound having anandamide activity.

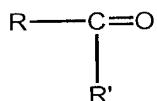
By way of example and not limitation, examples of the present invention will now be set forth.--

In the Claims:

Please amend Claims 1-2, 4-16 as follows:

1. A composition for oral administration, comprising a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament, wherein the precursor comprises an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, and having a moiety selected from the group consisting of methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, and seleno.

2. A composition according to claim 1 wherein the precursor is a long chain polyunsaturated fatty acid (LCPUFA) or derivative thereof of the general formula X:



wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R" is selected from the group consisting of -H, lower alkyl, -OH, NH₃, NHCH₂CH₂OH, and an acid addition salt or complex thereof.

4. A composition according to claim 2 wherein the precursor comprises a molecule having from 1 to 3 copies of formula X esterified to a glycerol backbone; in a stereochemical configuration selected from the group consisting of: *sn*-1,2,3; *sn*-1,2; *sn*-1,3; *sn*-2,3; *sn*-1; *sn*-2; and *sn*-3.

5. A composition according to claim 1 wherein the precursor comprises a fatty acid selected from the group consisting of arachidonate (20:4n-6 AA), linolenate (18:3n-6), gamma linolenate (18:3n-6), dihomogamma-linolenate (30:3n-6 DGLA), adrenic acid (22:4n-6), linolenate (18:3n-3), stearidonic (18:4n-3), eicosatetraenoic (20:4n-3), eicosapentaenoate (20:5n-3), docosahexaenoate (22:6n-3DHA), docosapentaenoate (22:5n-3 or 22:5n-6), tetracosapentaenoate (24:5n-3 or 24:5n-6), tetracosahexaenoate (24:6n-3) and Mead acid (30:3n-9).

6. A composition according to claim 1 wherein the precursor comprises arachidonate (20:4n-6 AA).

7. A composition according to claim 1 which comprises an inhibitor of an anandamide inactivating enzyme (amidase).

8. A composition according to claim 7 wherein the inhibitor is selected from the group consisting of oleate and oleamide, palmitate, palmitoylethanolamide, linoleylethanolamide, 2 palmitoylglycerol, and 2-linoleylglycerol.

9. A composition according to claim 7 wherein the inhibitor is palmitate or palmitoylethanolamide.

10. A composition according to claim 1 which comprises a triacylglycerol having palmitate and arachidonate attached to its backbone wherein arachidonate is at the *sn*-1 and *sn*-2 positions.

11. A composition according to claim 1 which comprises a compound which reacts with a CB receptor.

12. A composition according to claim 1 which comprises a steroid or non-steroidal anti-inflammatory drug (NSAID).

13. A composition according to claim 1 which comprises a physiologically acceptable carrier, diluent or adjuvant.

14. A method for producing a nutritional or therapeutic composition for oral administration comprising the steps of obtaining a therapeutically effective amount of a naturally occurring precursor that is metabolised to a compound having anandamide activity and preparing a composition including the precursor.

15. A method of manufacture a composition for the treatment or prevention of an anandamide-mediated ailment selected from the group consisting of hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception comprising the steps of preparing a composition comprising a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament, wherein the precursor comprises an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, and having a moiety selected from the group consisting of methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, and seleno.

16. A method of treating an anandamide-mediated ailment selected from the group consisting of hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma,

nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception which comprises administering to a patient having an anandamide-mediated ailment an effective amount of a composition comprising a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament, wherein the precursor comprises an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, and having a moiety selected from the group consisting of methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, and seleno.

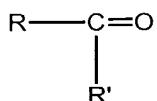
Please add newly-submitted Claims 17-25 as follows:

17. A method of preventing an anandamide mediated ailment selected from the group consisting of hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception comprising administering a therapeutically effective amount of a composition that is metabolised an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, and having a moiety selected from the group consisting of methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, and seleno to a patient in need of same.

18. A method of claim 14 wherein the method includes the step of purifying the naturally occurring precursor.

19. A method of claim 14 wherein the method includes the step of synthesizing the naturally occurring precursor.

20. A method according to claim 16 wherein the precursor is a long chain polyunsaturated fatty acid (LCPUFA) or derivative thereof of the general formula X:



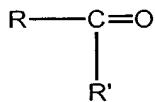
wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R" is selected from the group consisting of -H, lower alkyl, -OH, NH₃, NHCH₂CH₂OH, and an acid addition salt or complex thereof.

21. A method according to claim 16 wherein the precursor comprises a molecule having from 1 to 3 copies of formula X esterified to a glycerol backbone; in a stereochemical

configuration selected from the group consisting of: $sn-1,2,3$; $sn-1,2$; $sn-1,3$; $sn-2,3$; $sn-1$; $sn-2$; and $sn-3$.

22. A method according to claim 16 wherein the precursor comprises a fatty acid selected from the group consisting of arachidonate (20:4n-6 AA), linoleate (18:3n-6), gamma linolenate (18:3n-6), dihomogamma-linolenate (30:3n-6 DGLA), adrenic acid (22:4n-6), linolenate (18:3n-3), stearidonic (18:4n-3), eicosatetraenoic (20:4n-3), eicosapentaenoate (20:5n-3), docosahexaenoate (22:6n-3DHA), docosapentaenoate (22:5n-3 or 22:5n-6), tetracosapentaenoate (24:5n-3 or 24:5n-6), tetracosahexaenoate (24:6n-3) and Mead acid (30:3n-9).

23. A method according to claim 17 wherein the precursor is a long chain polyunsaturated fatty acid (LCPUFA) or derivative thereof of the general formula X:



wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R" is selected from the group consisting of -H, lower alkyl, -OH, NH₃, NHCH₂CH₂OH, and an acid addition salt or complex thereof.

24. A method according to claim 17 wherein the precursor comprises a molecule having from 1 to 3 copies of formula X esterified to a glycerol backbone; in a stereochemical configuration selected from the group consisting of: *sn*-1,2,3; *sn*-1,2; *sn*-1,3; *sn*-2,3; *sn*-1; *sn*-2; and *sn*-3.

25. A method according to claim 17 wherein the precursor comprises a fatty acid selected from the group consisting of arachidonate (20:4n-6 AA), linoleate (18:3n-6), gamma linolenate (18:3n-6), dihomogamma-linolenate (30:3n-6 DGLA), adrenic acid (22:4n-6), linolenate (18:3n-3), stearidonic (18:4n-3), eicosatetraenoic (20:4n-3), eicosapentaenoate (20:5n-3), docosahexaenoate (22:6n-3DHA), docosapentaenoate (22:5n-3 or 22:5n-6), tetracosapentaenoate (24:5n-3 or 24:5n-6), tetracosahexaenoate (24:6n-3) and Mead acid (30:3n-9).

REMARKS

This Preliminary Amendment is submitted in the above-identified patent application. Pursuant to a Preliminary Amendment, Claims 1, 3-10 and 12 have been amended. In addition, newly-submitted Claims 13-20 have been added and minor amendments have been made to the specification. This Preliminary Amendment does not add new subject matter.

Appl. No. PCT/EP00/08995

Applicants also note that the Preliminary Amendment is being made to place the claims in proper U.S. format and/or add new claims. Pursuant to the Preliminary Amendment, the claims are not being narrowed and therefore, Applicants do not disclaim any subject matter in view of this Preliminary Amendment.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Versions with Markings to Show Changes Made.**"

Respectfully submitted,

BELL, BOYD & LLOYD LLC



Robert M. Barrett
Reg. No. 30,142
P.O. Box 1135
Chicago, Illinois 60690-1135
Phone: (312) 807-4204

VERSION WITH MARKINGS TO SHOW CHANGES MADE**In the Specification:**

Please delete lines 1-3 and substitute therefor:

--SPECIFICATION**TITLE OF THE INVENTION****“NUTRITIONAL COMPOSITION”--**

On page 5, line 23, please add the following:

--SUMMARY OF THE INVENTION

The present invention provides improved nutritional and therapeutic compositions.--

On page 9, please delete lines 18-19 and substitute therefor:

--Additional features and advantages of the present invention will be described in and apparent from the detailed description of the presently preferred embodiments and the figures.

BRIEF DESCRIPTION OF THE DRAWINGS--

On page 10, line 19, please insert the following:

--DETAILED DESCRIPTION OF THE INVENTION

The present invention provides improved nutritional compositions. These compositions provide therapeutic benefits. The compositions include a naturally occurring precursor that is metabolized to a compound having anandamide activity.

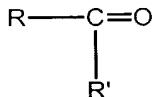
By way of example and not limitation, examples of the present invention will now be set forth.--

In the Claims:

Please amend Claims 1-2, 4-16 as follows:

1. (Amended) A [nutritional or therapeutic] composition for oral administration, [which comprises] comprising a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament, wherein the precursor comprises an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, and having a moiety selected from the group consisting of methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, [or a] and seleno[-moiety].

2. (Amended) A composition according to claim 1 wherein the precursor is a long chain polyunsaturated fatty acid (LCPUFA) or derivative thereof of the general formula X:



wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R" is selected from the group consisting of -H, lower alkyl, -OH, NH₃, [and] NHCH₂CH₂OH, [or] and an acid addition salt or complex thereof.

4. (Amended) A composition according to claim 2 [or 3] wherein the precursor comprises a molecule having from 1 to 3 copies of formula X esterified to a glycerol backbone; in a stereochemical configuration selected from the group consisting of: *sn*-1,2,3; *sn*-1,2; *sn*-1,3; *sn*-2,3; *sn*-1; *sn*-2; and *sn*-3.

5. (Amended) A composition according to [any preceding] claim 1 wherein the precursor comprises a fatty acid selected from the group [which comprises] consisting of arachidonate (20:4n-6 AA), linolenate (18:3n-6), gamma linolenate (18:3n-6), dihomogamma-linolenate (30:3n-6 DGLA), adrenic acid (22:4n-6), linolenate (18:3n-3), stearidonic (18:4n-3), eicosatetraenoic (20:4n-3), eicosapentaenoate (20:5n-3), docosahexaenoate (22:6n-3DHA), docosapentaenoate (22:5n-3 or 22:5n-6), tetracosapentaenoate (24:5n-3 or 24:5n-6), tetracosahexaenoate (24:6n-3) [or the] and Mead acid (30:3n-9).

6. (Amended) A composition according to [any preceding] claim 1 wherein the precursor comprises arachidonate (20:4n-6 AA).

7. (Amended) A composition according to [any preceding] claim 1 which comprises an inhibitor of an anandamide inactivating enzyme (amidase).

8. (Amended) A composition according to claim 7 wherein the inhibitor is selected from the group [which comprises] consisting of oleate and oleamide, palmitate, palmitoylethanolamide, linoleylethanolamide, 2 palmitoylglycerol, and 2-linoleylglycerol.

9. (Amended) A composition according to claim 7 [or 8] wherein the inhibitor is palmitate or palmitoylethanolamide.

10. (Amended) A composition according to [any preceding] claim 1 which comprises a triacylglycerol having palmitate and arachidonate attached to its backbone wherein arachidonate is at the *sn*-1 and *sn*-2 positions.

11. (Amended) A composition according to [any preceding] claim 1 which comprises a compound which reacts with a CB receptor.

12. (Amended) A composition according to [any preceding] claim 1 which comprises a steroid or non-steroidal anti-inflammatory drug (NSAID).

13. (Amended) A composition according to [any preceding] claim 1 which comprises a physiologically acceptable carrier, diluent or adjuvant.

14. (Amended) A method [of production of] for producing a nutritional or therapeutic composition for oral administration [which comprises] comprising the steps of [identifying, purifying or synthesising] obtaining a therapeutically effective amount of a naturally occurring precursor that is metabolised to a compound having anandamide activity and preparing a composition including the precursor.

15. (Amended) [Use of a composition according to any one of claims 1 to 13 in the] A method of manufacture [of] a [nutritional or therapeutic] composition for the treatment or prevention of an anandamide-mediated ailment selected from the group [which comprises] consisting of hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception comprising the steps of preparing a composition comprising a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament, wherein the precursor comprises an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, and having a moiety selected from the group consisting of methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, and seleno.

16. (Amended) A method of [treatment of] treating an anandamide-mediated ailment selected from the group [which comprises] consisting of hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception which comprises administering to a patient having an anandamide-mediated ailment an effective amount of a composition [according to any one of claims 1 to 13] comprising a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament, wherein the precursor comprises an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, and having a moiety selected from the group consisting of methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, and seleno.

Please add newly-submitted Claims 17-25 as follows:

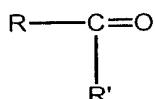
17. A method of preventing an anandamide mediated ailment selected from the group consisting of hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma,

nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception comprising administering a therapeutically effective amount of a composition that is metabolised an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, and having a moiety selected from the group consisting of methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, and seleno to a patient in need of same.

18. A method of claim 14 wherein the method includes the step of purifying the naturally occurring precursor.

19. A method of claim 14 wherein the method includes the step of synthesizing the naturally occurring precursor.

20. A method according to claim 16 wherein the precursor is a long chain polyunsaturated fatty acid (LCPUFA) or derivative thereof of the general formula X:

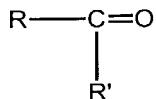


wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R" is selected from the group consisting of -H, lower alkyl, -OH, NH₃, NHCH₂CH₂OH, and an acid addition salt or complex thereof.

21. A method according to claim 16 wherein the precursor comprises a molecule having from 1 to 3 copies of formula X esterified to a glycerol backbone; in a stereochemical configuration selected from the group consisting of: *sn*-1,2,3; *sn*-1,2; *sn*-1,3; *sn*-2,3; *sn*-1; *sn*-2; and *sn*-3.

22. A method according to claim 16 wherein the precursor comprises a fatty acid selected from the group consisting of arachidonate (20:4n-6 AA), linoleate (18:3n-6), gamma linolenate (18:3n-6), dihomogamma-linolenate (30:3n-6 DGLA), adrenic acid (22:4n-6), linolenate (18:3n-3), stearidonic (18:4n-3), eicosatetraenoic (20:4n-3), eicosapentaenoate (20:5n-3), docosahexaenoate (22:6n-3DHA), docosapentaenoate (22:5n-3 or 22:5n-6), tetracosapentaenoate (24:5n-3 or 24:5n-6), tetracosahexaenoate (24:6n-3) and Mead acid (30:3n-9).

23. A method according to claim 17 wherein the precursor is a long chain polyunsaturated fatty acid (LCPUFA) or derivative thereof of the general formula X:



wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R" is selected from the group consisting of -H, lower alkyl, -OH, NH₃, NHCH₂CH₂OH, and an acid addition salt or complex thereof.

24. A method according to claim 17 wherein the precursor comprises a molecule having from 1 to 3 copies of formula X esterified to a glycerol backbone; in a stereochemical configuration selected from the group consisting of: *sn*-1,2,3; *sn*-1,2; *sn*-1,3; *sn*-2,3; *sn*-1; *sn*-2; and *sn*-3.

25. A method according to claim 17 wherein the precursor comprises a fatty acid selected from the group consisting of arachidonate (20:4n-6 AA), linoleate (18:3n-6), gamma linolenate (18:3n-6), dihomogamma-linolenate (30:3n-6 DGLA), adrenic acid (22:4n-6), linolenate (18:3n-3), stearidonic (18:4n-3), eicosatetraenoic (20:4n-3), eicosapentaenoate (20:5n-3), docosahexaenoate (22:6n-3DHA), docosapentaenoate (22:5n-3 or 22:5n-6), tetracosapentaenoate (24:5n-3 or 24:5n-6), tetracosahexaenoate (24:6n-3) and Mead acid (30:3n-9).

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Nutritional Composition

The present invention relates to a nutritional or therapeutic composition for oral
5 administration which comprises a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament or nutritional product, a method of production of the composition, use of the composition in the manufacture of a nutritional or therapeutic composition for the treatment or prevention of a behavioural disorder; and a method of treatment or prevention of a behavioural disorder which
10 comprises administering an effective amount of the composition.

Within the context of this specification the word "comprises" is taken to mean "includes, among other things". It is not intended to be construed as "consists of only".

15 Standard nomenclature for fatty acid compounds is used. For example, the number of carbon atoms and number and position of double bonds is typified by "20:4(5,8,11,14)" for arachidonic acid: the number preceding the colon is the total number of carbon atoms, the number immediately following the colon is the number of double bonds, and the numbers in parentheses are the position of the double bonds, starting from the end of
20 the chain bearing the carboxylic acid group. In all compounds referred to in this manner, except where otherwise indicated, all double bonds are cis.

Standard nomenclature for classes of fatty acid compounds is used indicating the location of the double bond closest to the methyl end group, typified by "n-3" or "n-6":
25 the number following the dash denotes the position of the double bond closest to the methyl end of the molecule, counting from the methyl end. Thus, arachidonic acid is in the n-6 class, as is linoleic acid (18:2(9,12)), whereas eicosapentaenoic acid (20:5(5,8,11,14,17)) is in the n-3 class. This nomenclature is equivalent to "omega or ω " nomenclature in the literature, " ω " and "n" being interchangeable.

5 Anandamide (also referred to as *N*-arachidonylethanolamine) is an example of an *N*-acyl ethanolamine (hereinafter referred to as NAE). Both NAEs and *N*-acyl amines (hereinafter referred to as NAAs), an example of the latter of which is oleamide, are naturally occurring in the human body. They have been found in the hippocampus, striatum, cerebellum, spleen, heart, plasma and cerebral spinal fluid as well as in human milk.

10 The term "anandamide activity" is used within the context of this specification to mean an activity selected from the group which comprises an activity attributed to the drug 9-tetrahydrocannabinol (THC), as well as affects specific to anandamide and 1- and 2-monoarachidonylglycerol isomers (hereafter denoted AG), and unique from THC. It has been suggested that anandamide and AG activities are typically, but not necessarily, mediated by binding to the receptor class, known as CB1 and CB2 receptors. These 15 anandamide activities include, but are not limited to: antinociception, catalepsy and inhibition of locomotor activity *in vivo* and displacement of 9-tetrahydrocannabinol (THC), inhibition of adenylate cyclase, inhibition of calcium channels, activation of phospholipase A₂, release of intracellular calcium *in vitro* and inhibition of twitch response *ex vivo*.

20

The term anandamide, as used within the context of this specification, refers to an NAE, NAA or MAG having anandamide activity (as defined above). Accepted scientific nomenclature will be used in this specification when reference is made to specific acyl moieties of an NAE, NAA or MAG.

25

It is well known that pharmaceutical compounds have wide application for their calming effects and they may be used in the treatment of patients suffering from conditions such as hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, convulsions, loss of appetite, nausea, cramps, diarrhoea, asthma, nervousness, 30 aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, gut upsets, or spasms, poor motor control, tics, excessive stress, spasticity or

multiple sclerosis. However, a number of these compounds are not naturally occurring in nature and in view of this, patients may be reluctant to be administered them. In the light of this there is a need for the provision of new products which include naturally occurring precursors of compounds that have a nutritive or therapeutic effect, when 5 metabolised endogenously to active compounds with anandamide activity.

Furthermore, a problem with most commercially available drugs is that they give rise to side affects such as nausea, bloating, cramping, etc. Clearly there is a need for a composition which does not give rise to these side effects.

10

The method of administration of a nutritive or therapeutic compound is an important consideration. Intravenous or subcutaneous administration of drugs requires expertise, and compared to oral administration it is not as safe, convenient or acceptable to the patient. In the light of these concerns it is clear that there is a need for new nutritive or 15 therapeutic products which may be administered orally.

20

In addition to the problems set out above, infant formulae are generally constructed so that they resemble human milk as closely as possible, however a plurality of components in human milk are bioactive and, because of synergies among the components, the inclusion of only one or a few of them may not reproduce the bioactivity of human milk. In view of this, a problem which presently faces researchers lies in the formulation of infant formulae or weaning foods which have components that are present in human milk and which have an equivalent activity to human milk. The problem is compounded in view of the fact that not all of the components in human milk 25 have been identified and there are variations in the concentration of components which are present, possibly due to variations of mother's diets.

25

A further problem which faces nutritionists lies in the field of pet nutrition. Whereas some pets are aggressive, others are excessively timid. Muzzles have been provided 30 which fit over the heads of aggressive animals and cover their mouths. This may not be a good solution in view of the fact that a muzzle may serve to aggravate the animal. In

the light of this, there is a need for alternative solutions for calming excessively aggressive or timid pets.

US 5874459 discloses that anandamide may act as a ligand which interacts with cannabinoid receptors in the central nervous system and gut (CB1 receptors) and/or immune cells and tissues such as spleen, thymus and lymphocytes (CB2 receptors). Furthermore, this document indicates that interactions between anandamide and these two types of cannabinoid receptors have been shown to induce physiological effects. It is described that non-arachidonyl NAEs and NAAs have been shown to inhibit anandamide inactivating enzyme. This inhibition has the net effect of potentiating the effect of anandamide.

It has been suggested that a family of NAEs and NAAs as well as *sn*-1 and *sn*-2 monoarachidonyl glycerides are agonists of anandamide receptors (here anandamide receptor refers to a receptor that anandamide might bind to, including CB1, CB2, non-CB receptors) and elicit responses analogous to that elicited by anandamide. The chemical structures of NAEs and NAAs are based on fatty acids and depending on the specific fatty acids esterified they have been shown to have different activities. For example, whereas anandamide interacts with both the CB1 receptor of the central nervous system and the CB2 receptor of the immune system, palmitolyethanolamide may interact with the CB2 receptor but not the CB1 receptor and has an anti-inflammatory effect but no known neural effect.

Nature, vol 396, page 636, (1998) discloses the results of an analysis wherein NAEs and 2 arachidonoylglycerol (2-AG) were identified from foods including human, bovine and goat milk and cocoa at various stages of processing. The document suggests that anandamide ($300\text{mgkg body weight}^{-1}$) and 2-arachidonyl glycerol ($400\text{mgkg body weight}^{-1}$) have bioactivity when taken *orally* in mice, however the compounds were active only at very high concentrations relative to the concentrations normally present in foods and the results obtained show that the amounts of anandamide, 2-AG and oleamide in foods, including milk and cocoa, are several orders of magnitude below

those required if administered by mouth, to reach the blood and cause observable "central effects". However, the document indicates that pure doses of anandamide, 2-AG and oleamide have calming effects and effects on the immune system when *injected* into animals. Calming effects are characterised by lessened activity, decreased 5 nociception and greater propensity for sleep.

US 568955 discloses that synthetically produced polyunsaturated fatty acid amides and their derivatives are able to mimic the effect of naturally occurring anandamides in the brain and bind to the cannabinoid receptor. The compounds described exhibit 10 physiological activity and are reported as being useful active ingredients in pharmaceutical compositions for treatment of inflammation, migraines, spasticity, glaucoma and multiple sclerosis.

Remarkably it has now been found that a composition for oral administration may be 15 provided which includes a precursor that is metabolised endogenously to form a compound having anandamide activity. It is particularly surprising that a dietary precursor is selectively taken up by the CNS and selectively incorporated into the NAE pool to serve as a CB receptor-binding ligand. In addition, it is remarkable that a dietary precursor induces only a small change in the phospholipid acyl composition but induces 20 a large change in the NAE composition.

The invention addresses the problems set out above.

Accordingly, in a first aspect the invention provides a nutritional or therapeutic 25 composition for oral administration which comprises a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament or nutritive product.

In a second aspect the invention provides a method of production of a nutritional or 30 therapeutic composition for oral administration which comprises the steps of identifying, purifying or synthesising a naturally occurring precursor that is metabolised

to a compound having anandamide activity.

In a third aspect the invention provides use of a precursor which is metabolised to a compound having anandamide activity in the manufacture of a nutritional or therapeutic composition for the treatment or prevention of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception.

Vocalization is taken to mean disturbances in vocalisation and vocalization related to bonding behaviour, for example between an infant and mother. Such vocalisations are important in animal husbandry and in successful nurturing of the offspring by the mother in household pets. Further, such behaviours as chronic sustained crying in human infants may be treatable by oral administration of an embodiment of a composition according to the invention.

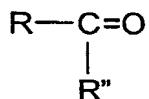
Oral administration of an embodiment of a composition according to the invention may also be used to treat or prevent inflammation in superficial mammal tissues (e.g., skin) by modulating levels of compounds with anandamide-like activity in these tissues.

In a forth aspect the invention provides a method of treatment of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception which comprises administering an effective amount of an embodiment of the

composition according to the invention.

Preferably the precursor that is metabolised to a compound having anandamide activity comprises a long chain polyunsaturated fatty acid (LCPUFA) or derivative thereof.

5 More preferably it comprises a compound of the general formula X:



wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R" is selected from -H, lower alkyl, -OH, NH₃, and NHCH₂CH₂OH, or an acid addition salt or complex thereof.

More preferably the precursor comprises a plurality of the formula X. Preferably 1-3 X molecules are esterified to a glycerol backbone, in the following stereochemical configurations: *sn*-1,2,3; *sn*-1,2; *sn*-1,3; *sn*-2,3; *sn*-1; *sn*-2; *sn*-3.

15

In an alternative embodiment the LCPUFA is a polyunsaturated fatty acid of 16-28 carbon atoms with 2-6 double bonds, having methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, and seleno- moieties.

20

More preferably the fatty acid is selected from the group which comprises arachidonate (20:4n-6 AA), linoleate (18:3n-6), gamma linolenate (18:3n-6), dihomogamma-linolenate (20:3n-6 DGLA), adrenic acid (22:4n-6), linolenate (18:3n-3), stearidonic (18:4n-3), eicosatetraenoic (20:4n-3), eicosapentaenoate (20:5n-3), docosahexaenoate (22:6n-3DHA), docosapentaenoate (22:5n-3 or 22:5n-6), tetracosapentaenoate (24:5n-3 or 24:5n-6), tetracosahexaenoate (24:6n-3) or the Mead acid (20:3n-9).

25

Preferably, an embodiment of a composition according to the invention includes an inhibitor of anandamide inactivating enzyme (also known as amidase). Preferably the

inhibitor is selected from the group which comprises oleate and oleamide, palmitate, palmitoylethanolamide, linoleylethanolamide, 2 palmitoylglycerol, 2-linoleylglycerol.

Preferably an embodiment of a composition according to the invention comprises a mixture of a saturated molecule in combination with an unsaturated precursor that is metabolised to a compound having anandamide activity. Preferably, the saturated molecule is palmitate or palmitoylethanolamide. Preferably the unsaturated precursor is arachidonic acid. This provides the advantage that the anandamide activity of the metabolite formed endogenously is potentiated by both inhibiting the breakdown of a metabolite having anandamide-like activity and by the saturated NAE compound binding to the CB2 receptor.

Preferably, an embodiment of a composition according to the invention comprises a mixture of a compound which reacts with a CB receptor in combination with a precursor that is metabolised to a compound having anandamide activity and an inhibitor of the amidase. This provides the advantage of synergy between the active molecules and potentiation of their effect by inhibiting the breakdown of a metabolite having anandamide-like activity.

Preferably, the precursor that is metabolised to a compound having anandamide activity is a free fatty acid, fatty acid ester of an alcohol, or a triacylglycerol. More preferably it is a triacylglycerol having an active fatty acid at the *sn*-1 and *sn*-2 position. This provides the advantage that it leads to particularly effective CB receptor agonism. Most preferably, the triacylglycerol comprises both the active precursor compounds (eg arachidonate) and the potentiator compounds (eg palmitate). This provides the advantage of a particularly effective mixture.

Preferably, an embodiment of a composition according to the invention comprises a structured triacylglycerol prepared by the interesterification of triacylglycerols with active fatty acids so that a bioactive fatty acid is found in the *sn*-2 position of the triacylglycerol. This provides the advantage of optimising delivery of the active FA to

body tissues, particularly the brain.

Preferably an embodiment of a composition according to the invention comprises a physiologically acceptable carrier diluent or adjuvant.

5

Preferably an embodiment of a composition according to the invention comprises a combination of a naturally occurring precursor that is metabolised to a compound having anandamide activity together with a typical steroidal or non-steroidal anti-inflammatory drug (NSAID). This provides the advantage that synergy occurs since the

10

combination has the ability to diminish inflammation via different pathways.

15

Preferably, an embodiment of a composition according to the invention comprises a precursor of a CB1 receptor agonist (e.g. anandamide) in combination with a precursor of a CB2 receptor agonist (e.g. palmitoylethanolamide). This provides the advantage that the anti-pain effect of the metabolites is about 100 times stronger than the effect provided by the metabolites of either precursor individually.

Embodiments of the invention will now be described in further detail with reference to the accompanying drawings in which:

20

Figure 1 shows the chemical structure of *N*-arachidonyl ethanolamine (anandamide), 2-AG, and oleamide.

25

Figure 2 shows the effects of oral cannabimimetic lipids on ambulation, rearing, immobility and analgesia.

30

Figure 3 shows the effects of oral administration of olive oil, anandamide, 2-AG, THC and oleamide on ambulation, rearing, immobility and analgesia. Ambulation, rearing, and immobility parameters were statistically, significantly different between the treatment groups and the control group, $p<0.01-0.05$, ANOVA, Newman-Keuls; Only THC statistically, significantly increased analgesia.

Figure 4 shows the effect of olive oil, anandamide, 2-AG, THC and oleamide on body temperature. All groups were statistically, significantly different from the control group, p<0.01-0.05, ANOVA, Newman-Keuls.

5

Figure 5 shows the effect of olive oil, anandamide, 2-AG, THC and oleamide on faecal output. Only the THC group was statistically, significantly different from the control.

10

Figure 6 shows the changes in piglet brain *N*-acylethanolamines following dietary fatty acid modification with a scale of 0 to 250 on the axis labelled pmols/mg piglet brain lipid extract. Bars within a group of three not denoted with a letter in common are statistically significant from one another (p<0.01-0.05, ANOVA, Newman-Keuls). Adeq, adequate.

15

Figure 7 shows the changes in piglet brain *N*-acylethanolamines following dietary fatty acid modification with a scale of 0 to 70 on the axis labelled pmols/mg piglet brain lipid extract. Bars within a group of three not denoted with a letter in common are statistically significant from one another (p<0.01-0.05, ANOVA, Newman-Keuls). Adeq, adequate.

20

Piglets were fed using two different kinds of adapted infant formulations supplemented with low levels of arachidonate and docosahexaenoate (approximately the same levels as found in human breast milk) and obtained from different sources (see Table 1). The levels of NAE, MAG (monoacylglycerol) and primary amides were evaluated in their brains.

25

In this study piglets were fed from birth to 18 days with diets comprising embodiments of a composition according to the invention with or without 0.5% 20:4n-6 from single cell oils and 0.4% 22:6n-3 in formula, with either low (deficient) 18:2n-6(1.6%) and 18:3n-3(0.1%), or with adequate 18:2(n-6)(15.6%) and 18:3n-3(1.5%).

30

The diet compositions are shown in table 1.

Table 1 Formulas varied in n-3 and n-6 fatty acid content

Fatty Acid	18:2n-6 – 18:3n-3 deficient			18:2n-6 - 18:3n-3 adequate			
	No LCP	Egg+ fish Oil	Single cell oil	No LCP	Egg fish oil	+ single cell oil	Sow milk
g/100g fatty acids							
8:0	8.0	7.0	7.4	17.2	15.5	14.9	
10:0	6.7	5.9	6.5	13.5	12.6	13.0	
12:0	44.2	39.7	42.9	1.0	0.3	0.3	0.1
14:0	17.1	15.6	16.8	0.8	0.6	0.6	2.4
16:0	9.5	10.5	9.5	11.3	12.1	10.9	28.1
18:0	3.4	4.0	3.5	3.2	3.5	3.3	5.6
16:1	0.1	0.34	0.1	0.1	0.3	0.2	4.7
18:1	8.1	10.4	9.3	33.3	33.4	35.1	32.6
18:2n-6	1.6	3.8	1.9	15.6	16.0	16.4	20.4
18:3n-6	-	0.6	0.1	-	0.4	0.1	0.2
20:2n-6	-	-	-	-	-	-	0.4
20:3n-6	-	-	-	-	-	-	0.2
20:4n-6	-	0.1	0.4	-	0.1	0.4	0.7
22:4n-6	-	-	-	-	-	-	0.1
18:3n-3	0.1	0.5	0.1	1.5	1.8	1.6	2.3
20:5n-3	-	0.1	-	-	0.1	-	0.1
22:5n-3	-	-	-	-	-	-	0.6
22:6n-3	-	0.3	0.3	-	0.3	0.3	0.1

5

Changes in individual brain phospholipid classes that occurred after feeding were analysed.

The results showed that the addition of 20:4n-6 and 22:6n-3 to diets containing adequate levels of essential fatty acids (18:2n-6 and 18:3n-3) lead to an increase in 22:6n-3 in phosphatidyl choline; a decrease in 22:5n-6 in phosphatidyl ethanolamine; and no change in arachidonate (20:4n-6) in any of the phospholipid classes.

Thus, the small, unsubstantial increase seen in 22:6n-3 in phosphatidyl choline is consistent with the fact that the relevant diet had added 22:6n-3; however the lack of significant increase in arachidonate in any of the phospholipid classes examined indicates that added arachidonate is not incorporated into these phospholipid classes, but

rather is metabolised or inadequately transported to the brain.

The primary amides, oleamide and arachidonamide, and 18:3 NAE were not detected and are omitted from table 2, which shows the changes in levels of MAG and NAE expressed as pmols/mg lipid that occurred following feeding of the diets.

Table 2
Monacyl glycerols (MAG)

Group	C20:4n-6	C22:4n-6	C22:6n-3
Adequate	66.0	3.53	3.87
adequate + SCO	44.4	6.23	5.93
Sow fed	44.1	6.13	6.67

Table 3
N-acyl-ethanolamines (NAE)

Group	C16:0	C18:0	C18:1n-9	C18:2n-6
Adequate	114.87	27.90	27.00	8.57
adequate + SCO	149.93	63.87	15.97	2.90
Sow fed	95.07	3.13	1.40	9.80

10

Table 4
N-acyl-ethanolamines (NAE)

Group	C20:5n-3	C22:4n-6	C22:5n-3	C22:6n-3
	C20:4n-6			
Adequate	6.10	32.87	14.80	3.63
adequate + SCO	23.77	172.37	23.07	33.67
Sow fed	19.97	165.63	29.30	28.00
				15.77

15 MAG levels were not statistically significant for 20:4n-6 MAG, 22:4n-6 MAG and 22:6n-3 MAG in animals fed essential fatty acid sufficient diets (*sn*-1 and 2 isomers combined). This is an important finding because specific MAGs, such as 2-AG are

known to bind to CB receptors and have bioactivity.

In animals fed the 18:2n-6/18:3n-3 sufficient diets, supplementation with AA and DHA led to increases in 20:4n-6 NAE and 22:4n-6 NAE (22:4n-6 is the 2-carbon elongation product of AA), 22:6n-3 NAE, 20:5n-3 NAE and 22:5n-3 NAE (the latter two are retroconversion products of 22:6n-3). The levels of these NAE products were similar to that found in sow milk fed piglets. Thus, it is a remarkable feature of the invention that when sufficient essential fatty acids are provided in the diet, the supplementation of AA and DHA to levels found in breast milk, has the effect of increasing corresponding NAE products to levels found in sow milk.

The results obtained indicate that supplementation with AA and DHA to formulae having sufficient essential fatty acid had minimal effects on brain phospholipid acyl moieties. However, in striking contrast, the same level of supplementation led to a 4-fold increase in the level of 20:4n-3 NAE present, a 5.2 fold increase in 20:5n-3 NAE, and a 9.5 fold increase in 22:5n-3 and 22:6n-3 NAE.

In order to show the biological activity of the composition of the present invention on animal's behaviour the effect of dietary poly-unsaturated fatty acids with and without a CB-1 receptor antagonist on anxiolytic-like responses in mice were tested. To this end, the ELEVATED PLUS MAZE TEST was applied (adapted after Handley and Mithani (Naunyn. Schmied. Arch. Pharmacol. 327: 1-5, 1984).

For the experiments male Rj:NMRI mice, obtained from Elevage Janvier, Le Genest-Saint-Isle France and weighing 10-11 g at delivery and 33-51 grams on day 42 were used. The mice were housed 10 per cage in wire cages with bedding and normal light cycle. They received *ad libitum* quantities of bottled distilled water and purified powdered diets (7.5 g/mouse) in ceramic cups (10/group) for 42 days. The Food was maintained at -80 °C in daily aliquots under nitrogen, thawed each afternoon before administration to mice. Uneaten food was discarded daily.

The principle of the test resides in that anxiolytic agents increase the number of entries into the open and often the closed arms of the elevated. Consequently, mice should want to move and explore the spaces of the open and closed arms rather than staying still in the middle).

5

Mice were given the following agents intraperitoneally 60 minutes before the Plus Maze test:

Tween 80 as placebo;

the anxiolytic agent Clobazam at a non-sedative dose for test validation; or

10 validated amounts of AM251 (Tocris Cookson LTD., UK), a CB-1 receptor antagonist, to inhibit binding of endogenous NAEs to the CB-1 receptor.

15 All diets contained 90% fat-free AIN93G rodent diet in powder form (Lot 9350-5, Dyets, Inc., Bethlehem, PA), 0.4% milk fat, 1.2% palm olein, 1.9% Trisun sunflower oil, 1.5% soybean oil and 2.1-5.1% medium chain triacylglycerol oil. Parts of the medium chain triacylglycerol oil were replaced with 1.1% algal oil (providing 0.5 dietary wt.-% arachidonic acid) in diet D, 1.9% fish oil (providing 0.5 dietary wt.-% docosahexaenoic acid) in diet E, and with 1.1% algal oil and 1.9% fish oil in diets F and G. Dietary groups are summarized in the table below:

20

	Diet Code	Diet Description	Agent given before Plus Maze Test
25	A	Control Diet	Tween 80, 1% distilled water solution
	B	Control Diet	Clobazam, 32 mg/kg body weight
	C	Control Diet	AM 251, 64 mg/kg body weight
	D	Diet AA	Tween 80, 1% distilled water solution
	E	Diet DHA	Tween 80, 1% distilled water solution
	F	Diet AA+DHA	Tween 80, 1% distilled water solution
30	G	Diet AA+DHA	AM 251, 64 mg/kg body weight

Abbreviations: AA, arachidonic acid; DHA, docosahexaenoic acid

The body weight, weight gain and the food intake of the mice was monitored throughout the experiment. These parameters were not significantly affected by ingestion of the various diets using classical one way analysis of variance (ANOVA). This indicates that differences in the behavioral tests as found can only be attributed to the components in

35

the diet that were varied, namely dietary polyunsaturated fatty acids. To assess changes in the Plus Maze test, generalized Linear Models (GLM) and the *Poisson* family were used because the obtained response data are non-normally distributed counts.

5 Number of Entries in the Closed Arms

A vs. B: Average entries were 3.6 and 6.3, respectively, and the difference is at the limit of statistical significance (*p*-value = 0.053). This result establishes that the anxiolytic agent Clobazam, under the present conditions, can increase closed arm entries.

10 A vs. C: There was no significant difference (*p*-value = 0.19).

A, D, E and F: overall, the *p*-value is 0.06. The fitted average entries are respectively 3.6, 6.4, 6.0 and 6.8. In group D, there is one mouse with 16 entries, which is unusually high. Omitting this mouse, the *p*-value becomes 15 significant (0.02) and the prediction for group

D decreases to 5.3. This result establishes that the combination of dietary AA and DHA may induce anxiolytic (Clobazam-like) effects.

20 F vs. G: Average entries are respectively 6.8 and 4.6, and the difference is at the limit of statistical significance (*p*-value = 0.11). This result indicates that the anxiolytic effects of the combination of dietary AA and DHA may be transduced via CB-1 receptor binding, i.e., via binding of PUFA-derived NAEs.

25 C vs. G: Average entries are respectively 2.3 and 4.6, and the difference is close to statistical significance (*p*-value = 0.08). This result indicates that CB-1 receptors are not the only receptors that mediate responses in the PLUS MAZE TEST, i.e., non-CB-1 receptors may partially mediate the actions of dietary PUFA and (PUFA-derived) NAEs. Additionally, the 30 drug AM251 may not fully antagonize CB-1 receptor binding.

In summary, the results from the number of entries into the closed arms in the

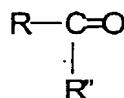
ELEVATED PLUS MAZE TEST show that dietary AA and DHA and the combination of the two, have anxiolytic-like effects that seem to be mediated via their conversion to NAEs, and these NAEs in turn bind to CB-1 receptors located in brain regions known to induce behavioral responses in the PLUS MAZE TEST, such as the hippocampus.

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It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is 10 therefore intended that such changes and modifications be covered by the appended claims.

Amended claims

1. A nutritional or therapeutic composition for oral administration, which comprises a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament, wherein the precursor comprises an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, having a methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, or a seleno-moiety.
2. A composition according to claim 1 wherein the precursor is a long chain polyunsaturated fatty acid (LCPUFA) or derivative thereof of the general formula X:



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wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R" is selected from -H, lower alkyl, -OH, NH₃, and NHCH₂CH₂OH, or an acid addition salt or complex thereof.

15

3. A composition according to claim 2 wherein the precursor comprises a molecule having a plurality of formula X.
- 20 4. A composition according to claim 2 or 3 wherein the precursor comprises a molecule having from 1 to 3 copies of formula X esterified to a glycerol backbone; in a stereochemical configuration selected from: *sn*-1,2,3; *sn*-1,2; *sn*-1,3; *sn*-2,3; *sn*-1; *sn*-2; *sn*-3.

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5. A composition according to any preceding claim wherein the precursor comprises a fatty acid selected from the group which comprises arachidonate (20:4n-6 AA), linoleate (18:3n-6), gamma linolenate (18:3n-6), dihomogamma-linolenate (20:3n-6 DGLA), adrenic acid (22:4n-6), linolenate (18:3n-3), stearidonic (18:4n-3), eicosatetraenoic (20:4n-3), eicosapentaenoate (20:5n-3), docosahexaenoate (22:6n-3DHA), docosapentaenoate (22:5n-3 or 22:5n-6), tetracosapentaenoate (24:5n-3 or 24:5n-6), tetracosahexaenoate (24:6n-3) or the Mead acid (20:3n-9).
10
6. A composition according to any preceding claim wherein the precursor comprises arachidonate (20:4n-6 AA).
15
7. A composition according to any preceding claim which comprises an inhibitor of an anandamide inactivating enzyme (amidase).
20
8. A composition according to claim 8 wherein the inhibitor is selected from the group which comprises oleate and oleamide, palmitate, palmitoylethanolamide, linoleylethanolamide, 2 palmitoylglycerol, 2-linoleylglycerol.
25
9. A composition according to claim 8 or 8 wherein the inhibitor is palmitate or palmitoylethanolamide.
30
10. A composition according to any preceding claim which comprises a triacylglycerol having palmitate and arachidonate attached to its backbone wherein arachidonate is at the *sn*-1 and *sn*-2 positions.
11. A composition according to any preceding claim which comprises a compound which reacts with a CB receptor.
12. A composition according to any preceding claim which comprises a steroid or

non-steroidal anti-inflammatory drug (NSAID).

13. A composition according to any preceding claim which comprises a physiologically acceptable carrier, diluent or adjuvant.

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14. A method of production of a nutritional or therapeutic composition for oral administration which comprises the steps of identifying, purifying or synthesising a naturally occurring precursor that is metabolised to a compound having anandamide activity.

10

15. Use of a composition according to any one of claims 1 to 14 in the manufacture of a nutritional or therapeutic composition for the treatment or prevention of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception.

15

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16. A method of treatment of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception which comprises administering an effective amount of a composition according to any one of claims 1 to 14.

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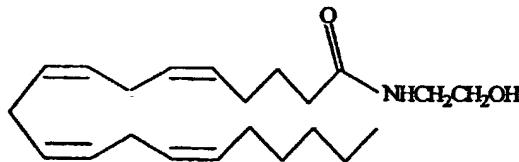
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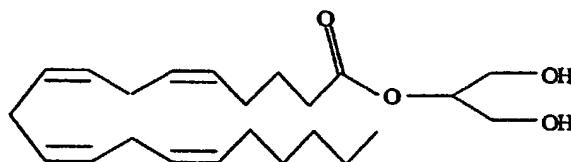
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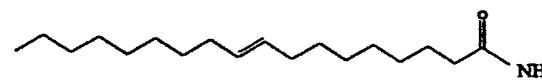
(54) Title: NUTRITIONAL COMPOSITION



Anandamide



2-AG

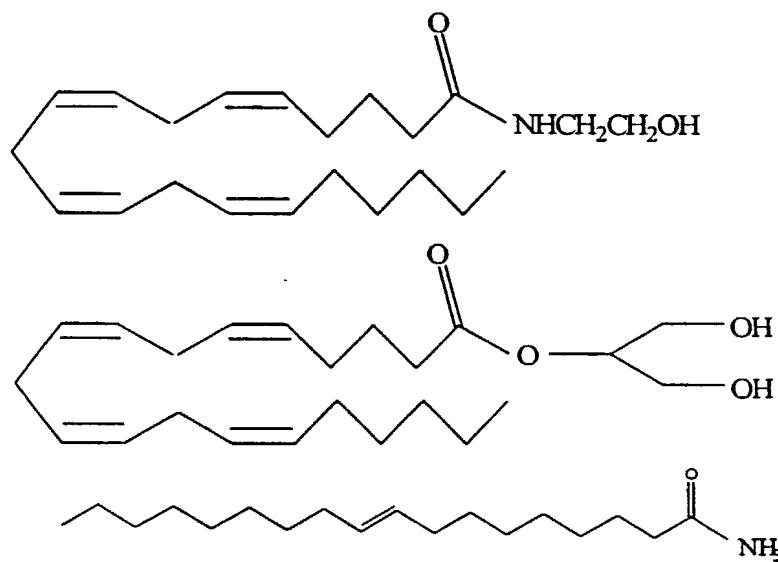


Oleamide

(57) Abstract: A nutritional or therapeutic composition for oral administration which comprises a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament or nutritive product. In addition the invention includes a method of production of the composition, use of the composition in the manufacture of a nutritional composition for the treatment or prevention of a behavioural disorder, and a method of treatment or prevention of a behavioural disorder which comprises administering an effective amount of the composition. In a preferred embodiment the composition comprises a triacylglycerol having palmitate and arachidonate attached to its backbone wherein arachidonate is at the *sn*-1 and *sn*-2 positions.

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Fig. 1



Anandamide

2-AG

Oleamide

Ambulation, No squares
crossed

Fig. 2

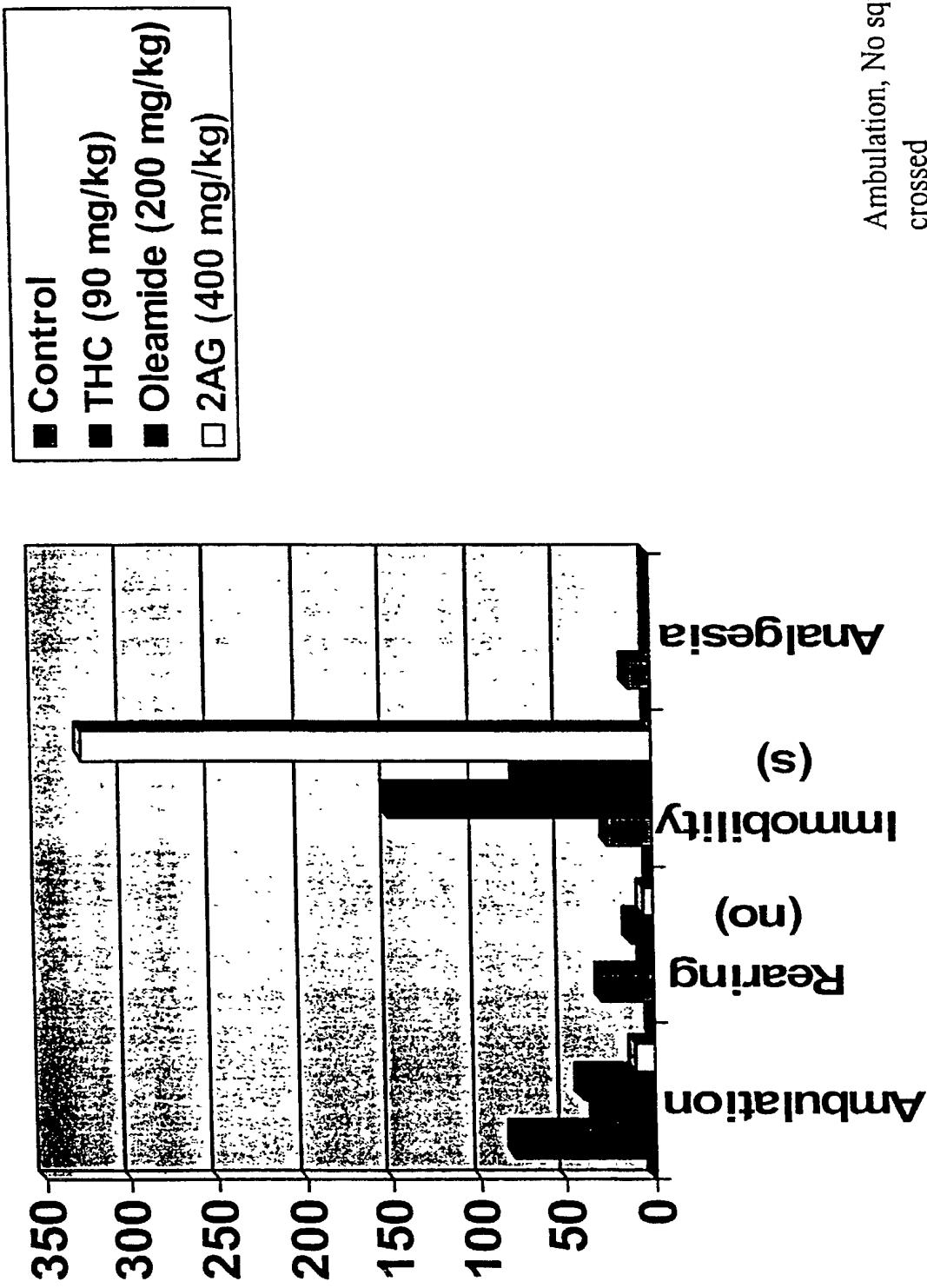


Fig. 3

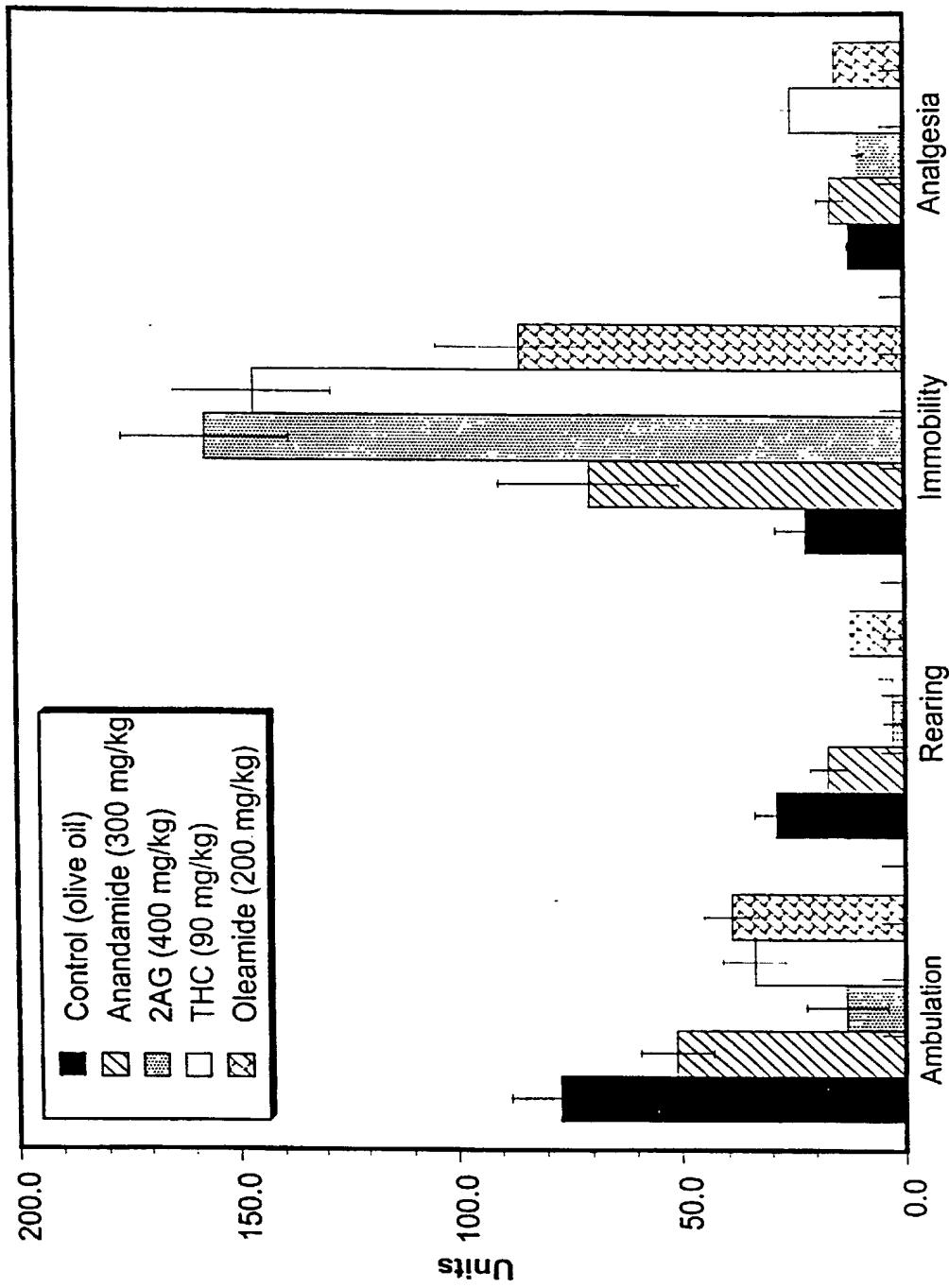


Fig. 4

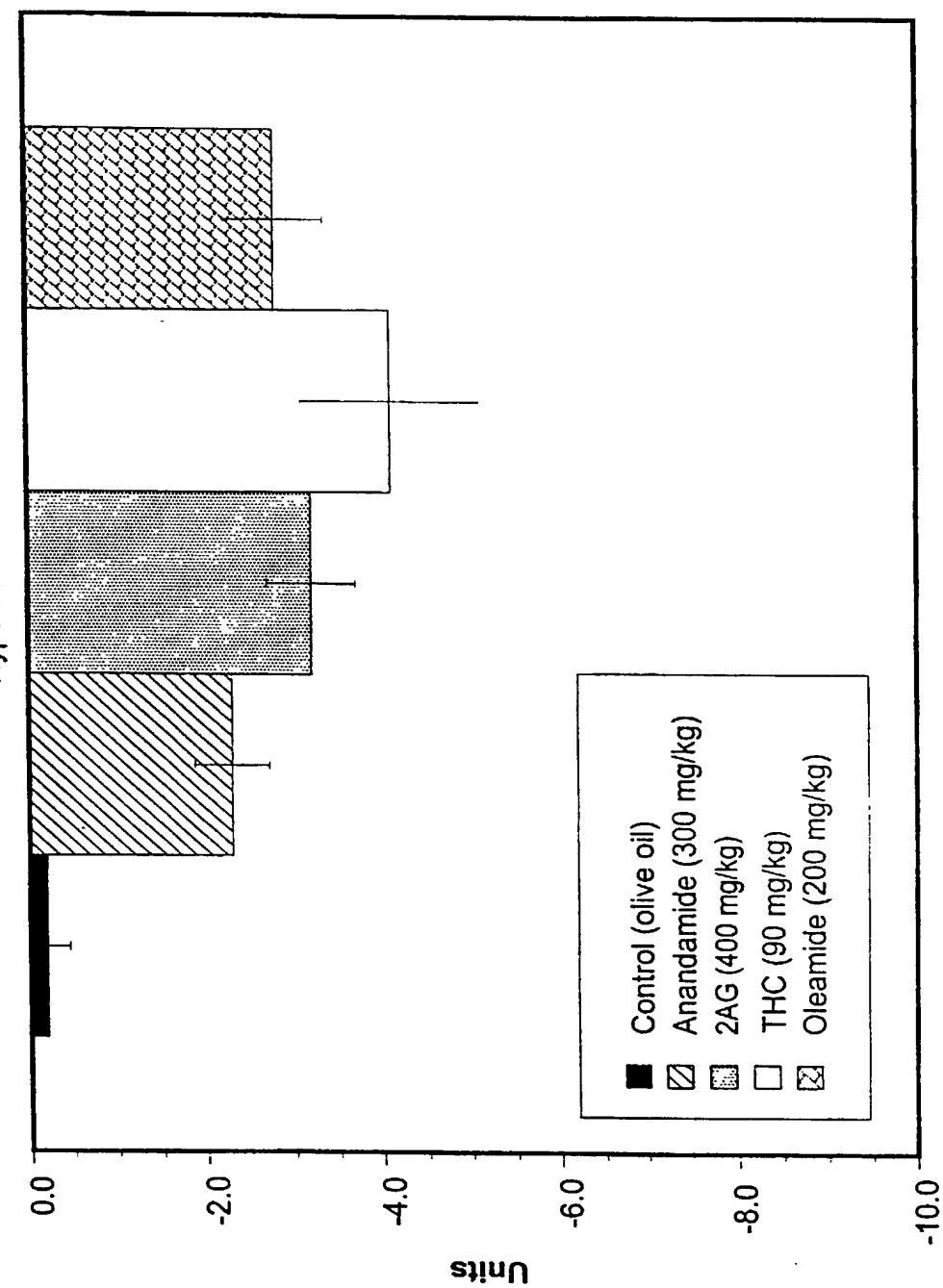


Fig. 5

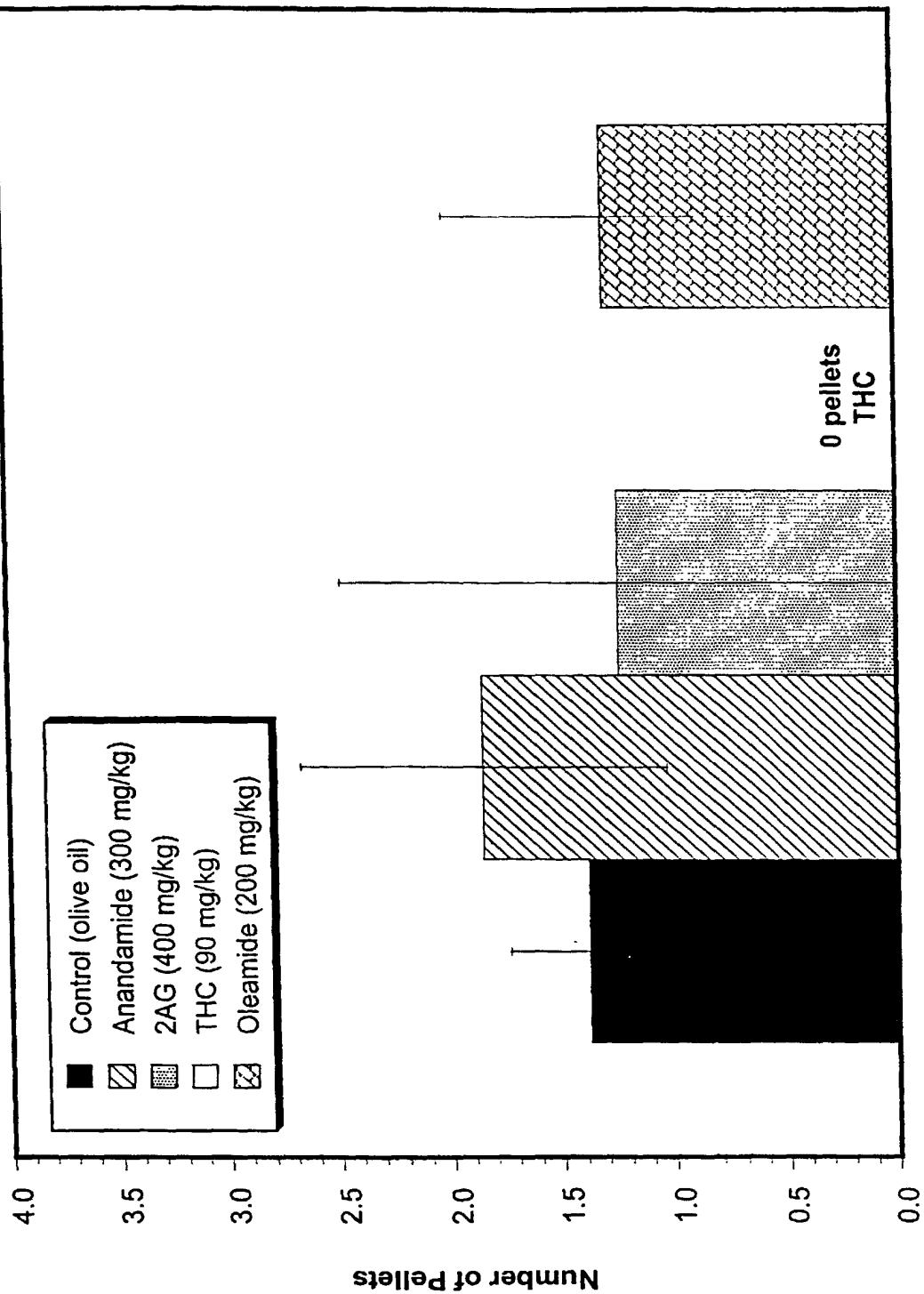


Fig. 6

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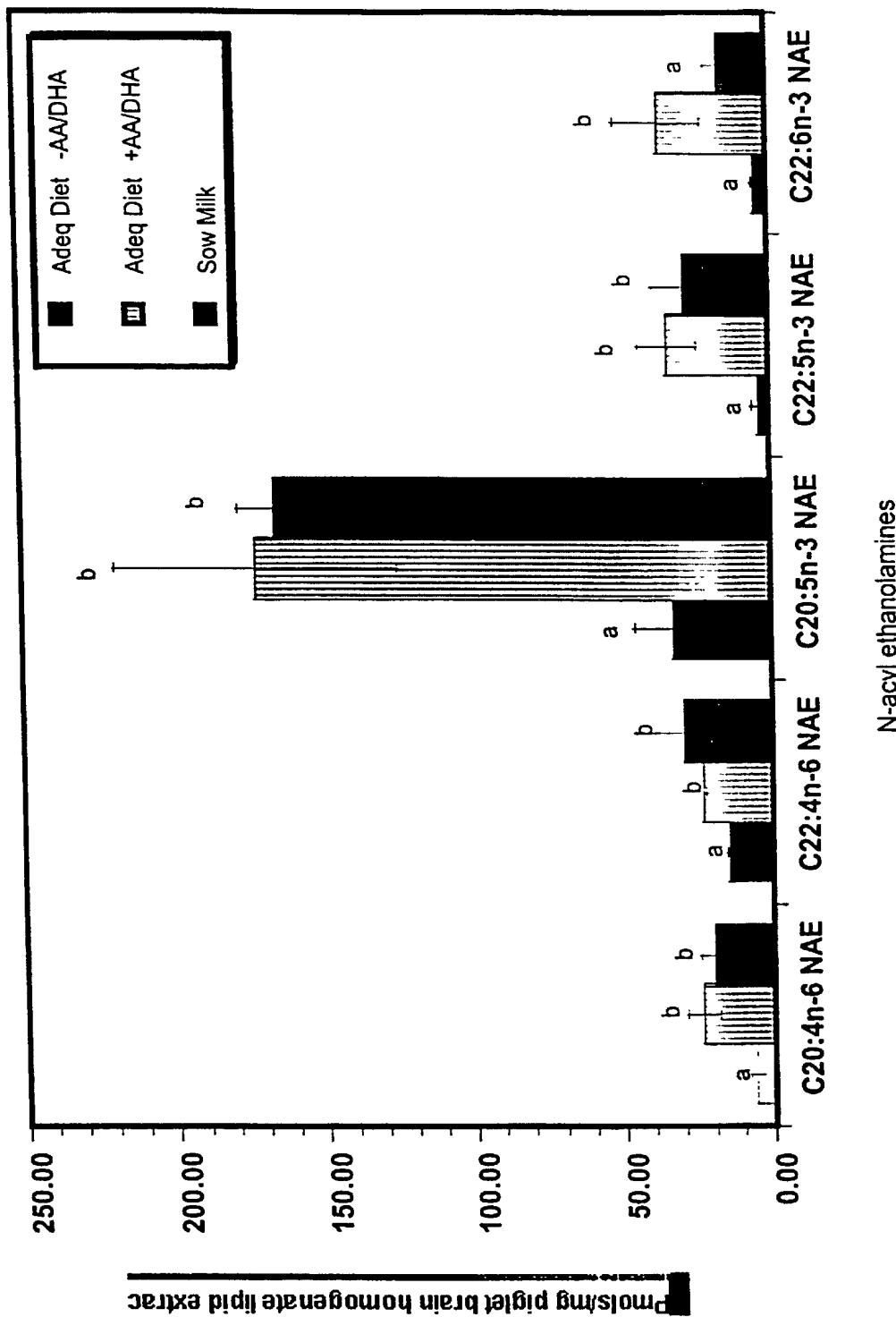
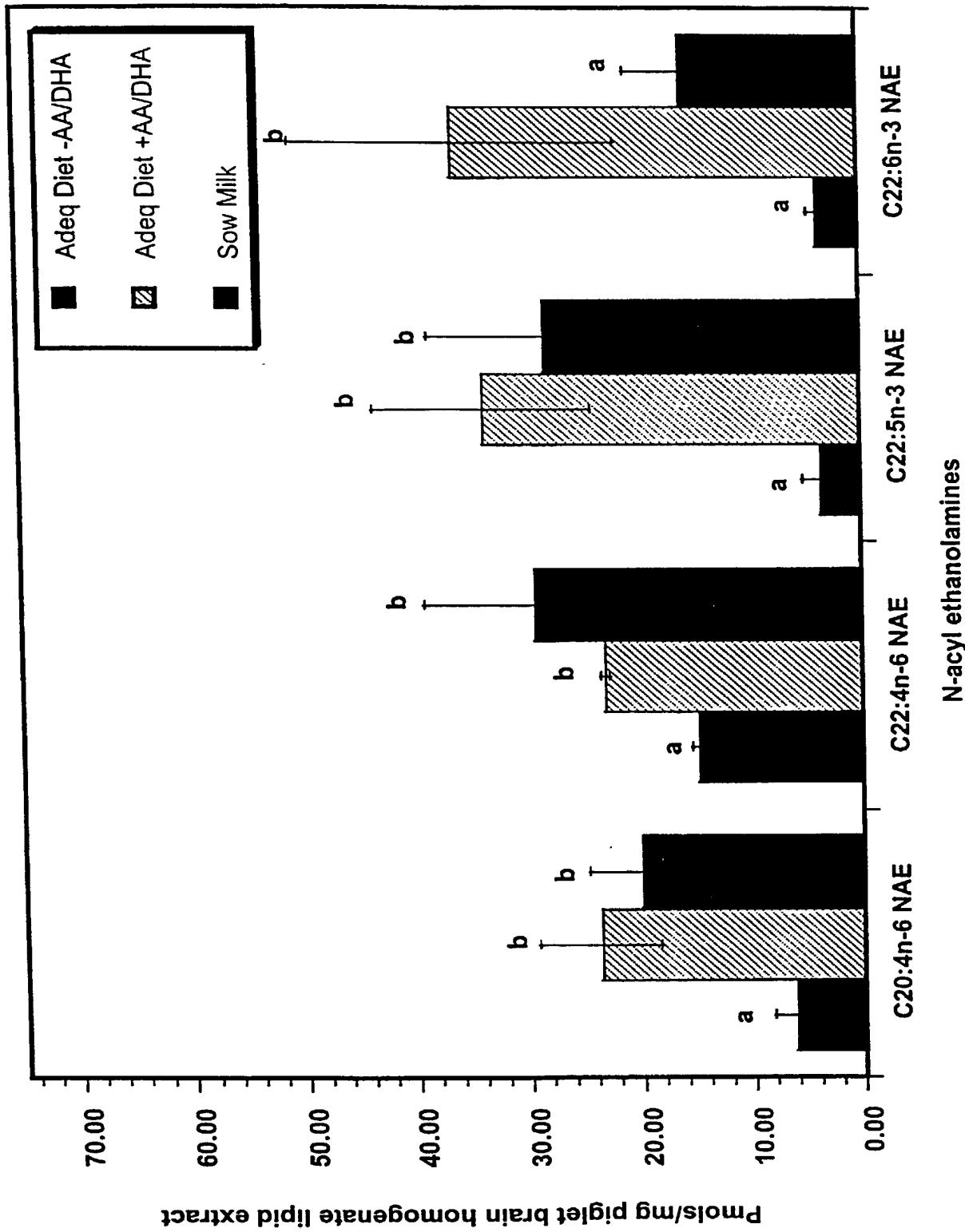


Fig. 7



DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NUTRITIONAL COMPOSITION

the specification of which: (check one)

is attached hereto.

was filed on 14 September 2000, as United States Application No. or PCT International Application No. PCT/EP00/08995 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent Office all information which is known to me to be material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Day/Month/Year Filed	Priority Not Claimed
9923738.0	Great Britain	07.10.1999	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

Application Serial No.	Filing Date
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I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status
		(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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And all telephone calls be directed to: (312) 807-4204.

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